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EXAMINER	
STEADMAN, DAVID J	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,951	ANDERTON ET AL.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-29,31-36,38-46,53 and 54* is/are pending in the application.

4a) Of the above claim(s) *31,33-35,40,43-46,53 and 54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-29,32,36,38,39,41 and 42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/20/06, 6/1/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Appendices A&B*.

DETAILED ACTION

Status of the Application

[1] Claims 22-29, 31-36, 38-46, and 53-54 are pending in the application.

[2] Applicant's amendment to the claims, filed on 7/10/08, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims. The amendment cancels claims 30, 37, and 50-52 and amends claims 22, 31-32, 36, 44, and 54.

Election/Restriction

[3] Applicant's election with traverse of Group II, claims 22-32, 36-42, and 51, drawn to a method of screening for inhibitors of Tau protein phosphorylation by a kinase including CK1 using a substrate other than Tau protein, and the species of S289 and mass spectroscopy, in the reply filed on 7/10/08 is acknowledged.

Beginning at p. 6 of the 7/10/08 remarks, applicant traverses the lack of unity requirement among groups I-III on the ground(s) that:

> The examiner alleged that the shared technical feature of Groups I to VII is a method of screening for substances that inhibit tau phosphorylation by CK1, and that this technical feature is shown, by Kuret et al., to lack novelty or inventive step. In the claims as currently amended, the shared technical feature is at least a method for screening substances which inhibit Tau phosphorylation by CK1 at specified phosphorylation sites.
>
> The disclosure of Kuret at al. is concerned with providing data which may imply that CK1 a isoforms are involved in the formation of hyperphosphorylated tau

in neurodegenerative disease, for example due to the tight association of these isoforms with tau pathology. The conclusions reached in this reference are presented as speculative or putative conclusions: the presented data are said to be "consistent with" CK1 a playing a role in tau phosphorylation. For example, at page 2513, left column lines 41-43 it is stated that "the subceUular distribution of CK1 a immunoreactivity is consistent with a role in tau phosphorylation".

In addition to the speculative tone of Kuret et al., it is noted that nowhere in this reference is the screening method for inhibitors of tau phosphorylation by CK1 disclosed or even contemplated. Additionally, there is no disclosure or suggestion of a method for detecting phosphorylation of tau by CK1 at specific sites in the Tau protein, nor of sites which allow for the detection of phosphorylation by CK1 in the absence of other kinases. Furthermore, there is certainly no disclosure of the particular specific sites recited in claim 22, nor a method of screening for an inhibitor ofphosphorylation oftau by CK1 at these sites. Likewise, none of these features is disclosed by Singh et al. Therefore, the shared technical feature of the claims is not disclosed or suggested in the cited references.

For the above-stated reasons, it can be seen that the shared technical feature of the claims is novel and non-obvious when considered in light of the prior art. Therefore, the subject matter of claim 22 and its dependent claims are linked by a single inventive concept as required by PCT Rule 13.1. The restriction requirement dividing claim 22 among Groups I-hi should, therefore, be withdrawn.

Regarding the other claims, it is noted that claims 50 to 52 have been deleted in the claim set currently presented. Claim 46, directed to a substance obtained by the method of claim 22 is unified with the currently presented claims as it is produced by a method employing the special technical feature. In addition, it provides the same advantages as the method, for example in the treatment of AD and related

> diseases, and in the investigation of the mechanism of such diseases. Claims 53 and 54 are directed to methods of medical treatment employing a substance obtained by the method of claim 22. These claims also are unified with the other claims currently presented, as they have the same technical feature and advantages as discussed above. Claim 45 is unified with the other claims for similar reasons.

Applicant's argument is not found persuasive. At least for reasons set forth below, the claimed invention is shown by the combination of Chijiwa, Lau, Castro, Singh, and Kuret to lack an inventive step and thus the technical feature of Group II is not a contribution over the prior art. Consequently, the inventions of Groups I-VII lack unity of invention and the requirement is still deemed proper and is therefore made FINAL.

[4] According to applicant, "Claims 22-29, 32, 36 and 38-42 are believed to read on the elected subject matter" (instant remarks at p. 8, bottom). However, it is noted that claim 40 is drawn solely to the non-elected species of site specific recognition reagent. Accordingly, claims 31, 33-35, 40, 43-46, and 53-54 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 7/10/08.

[5] Claims 22-29, 32, 36, 38-39, and 41-42 are being examined on the merits. Claims 22, 32, and 39 are being examined only to the extent the claims read on the elected subject matter.

Claim to Priority

[6] This application is a national stage filing of PCT/GB04/02739, filed on 6/25/04, which claims priority under 35 U.S.C. § 119(a) to (d) to UK application 0314943.2, filed on 6/25/03. A certified copy of the foreign priority document was filed in the instant application on 12/23/05.

Information Disclosure Statement

[7] All references cited in the information disclosure statements (IDSs) filed on 4/20/06 and 6/1/06 have been considered by the examiner. A copy of Forms PTO/SB/08 is attached to the instant Office action.

[8] If the examiner has inadvertently overlooked an IDS in the application file, applicant is kindly requested to alert the examiner to this oversight in the response to this Office action.

Specification/Informalities

[9] The listing of references in the specification at pp. 46-47 is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609.04(a) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

[10] The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: ---Method for Screening for Inhibitors of Tau Phosphorylation by Casein Kinase I---.

Claim Objections

[11] Claim 27 is objected to as not ending with a period. Appropriate correction is required.

[12] Claim 28 is objected to in the recitation of "full tau protein" and in order to improve claim form, it is suggested that the noted phrase be amended to recite "full length tau protein".

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[13] Claims 25 and 29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claims 25 and 29 recite the limitations "the nucleic acid molecule" in line 1. There is insufficient antecedent basis for this limitation in the claims.

[b] Claims 25 and 29 are indefinite in the recitation of "stringent conditions" as the specification does not define what conditions constitute "stringent". What hybridization

conditions are considered "stringent" varies widely in the art depending on the individual situation as well as the person making the determination. As such it is unclear how similar or dissimilar to the sequence of a nucleic acid encoding SEQ ID NO:1 or 2 a sequence must be to be included within the scope of these claims. While it is acknowledged that the specification discloses exemplary "stringent conditions" (p. 18, lines 5-19), these are non-limiting and fail to provide an indication of the metes and bounds of those conditions that are considered to be "stringent". It is suggested that applicant clarify the meaning of the noted phrase.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[14] Claim(s) 22-29, 32, 36, 38-39, and 41-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

CLAIM INTERPRETATION: According to MPEP 2163.II.A.1, in evaluating a claimed invention for adequate written description, the examiner should determine what the claim as a whole covers. "Claim construction is an essential part of the examination

process. Each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description. See, e.g., *In re Morris*, 127 F.3d 1048, 1053-54, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997)."

According to the specification, "In the present invention, derivatives of the tau proteins, kinases (especially CK1 kinase...have an amino acid sequence which differs by one or more amino acid residues from the wild-type amino acid sequence, by one or more of addition, insertion, deletion and substitutions of one or more amino acids. Thus, variants, derivatives, alleles, mutants and homologues…are included" (p. 17, lines 10-17).

MPEP 2163.II.A.2.(a).i) states, "Whether the specification shows that applicant was in possession of the claimed invention is not a single, simple determination, but rather is a factual determination reached by considering a number of factors. Factors to be considered in determining whether there is sufficient evidence of possession include the level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention".

For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or

disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406. MPEP § 2163 states that a "representative number of species" means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

In accordance with the specification, the recited casein kinase 1 (CKI) and tau proteins encompass a genus that includes any and all mutants and variants having any alteration(s) relative to a known sequence. In this case, the specification discloses only a single representative species of casein kinase or tau proteins, *i.e.*, SEQ ID NO:1 and 2, respectively. Also, the prior art acknowledges naturally occurring CKI polypeptides from a variety of sources including, *e.g.*, human, bovine, yeast, and rat, as noted below. However, these representative species fail to reflect the variation among the genus of CKI and tau polypeptides as encompassed by the claims, particularly as neither the specification nor the prior art discloses a correlation between the structures of the CKI and tau polypeptides and the ability to maintain the function of CKI phosphorylation of tau. The recited CKI and tau proteins encompass widely variant species, particularly as the structures of the CKI and tau proteins are unlimited and include any number of amino acid variations.

Given the genus encompasses any mutants and variants of CKI and tau polypeptides, the lack of description of a representative number of species, and the lack

of a structure-function correlation, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[15] Claims 22-29, 32, 36, 38-39, and 41-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods using art-recognized CKI and tau proteins, does not reasonably enable methods using any and all variants of CKI and tau proteins as broadly encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

"The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue." *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). The Factors most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: According to MPEP 2164.04, "[b]efore any analysis of enablement can occur, it is necessary for the examiner to construe the claims…and explicitly set forth the scope of the claim when writing an Office action." Also, MPEP 2164.08 states, "[a]ll questions of enablement are evaluated against the claimed subject matter. The focus of the examination inquiry is whether everything within the scope of the claim is enabled. Accordingly, the first analytical step requires that the examiner determine exactly what subject matter is encompassed by the claims…claims are to be given their broadest reasonable interpretation that is consistent with the specification."

CLAIM INTERPRETATION: According to the specification, "In the present invention, derivatives of the tau proteins, kinases (especially CK1 kinase...have an amino acid sequence which differs by one or more amino acid residues from the wild-type amino acid sequence, by one or more of addition, insertion, deletion and substitutions of one or more amino acids. Thus, variants, derivatives, alleles, mutants and homologues…are included" (p. 17, lines 10-17). In accordance with the specification, the recited casein kinase 1 (CKI) and tau proteins encompass a genus that includes any and all mutants and variants having any alteration(s) relative to a known sequence.

The broad scope of recited CKI and tau proteins is not commensurate with the enablement provided by the disclosure as broadly encompassed by the claims. In this case the disclosure is limited to enabling methods using art-recognized CKI and tau proteins.

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: According to MPEP 2164.03, "what is known in the art provides evidence as to the question of predictability…in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims".

As noted below, the state of the art at the time of the invention acknowledges CKI from a variety of sources – bovine, yeast, rat, and human. However, it is noted that these polypeptides are naturally-produced or are recombinant versions of wild-type proteins. It was well-known in the prior art that the effects of modification(s) to a polypeptide are unpredictable, even those that are considered to be "conservative" substitutions. See, *e.g.,* MPEP 2144.08, which states, "The effect of a conservative substitution on protein function depends on the nature of the substitution and its location in the chain. Although at some locations a conservative substitution may be benign, in some proteins only one amino acid is allowed at a given position. For example, the gain or loss of even one methyl group can destabilize the structure if close packing is required in the interior of domains. James Darnell et al., Molecular Cell Biology 51 (2d ed. 1990)". Because the specificity of a kinase is dependent upon its amino acid sequence, it is highly unpredictable as to the effects of altering the amino acid sequence of a CKI polypeptide and still maintain the ability to phosphorylate tau protein. This is particularly important since the utility of the claimed invention is in identifying potential therapeutic inhibitors of *CKI,* not any kinase. Thus, the mutant and variant polypeptides should maintain the specificity of a biologically relevant CKI polypeptide. Similarly,

because the amino acid sequence of a kinase substrate determines whether or not it will be phosphorylated, it is highly unpredictable as to the effects of altering the amino acid sequence of a tau polypeptide and still maintain the its ability to be phosphorylated by CKI.

The amount of direction provided by the inventor; The existence of working examples: According to MPEP 2164.03, "if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling".

The specification discloses a single working example of a CKI and tau polypeptide, *i.e.*, SEQ ID NO:1 and 2, respectively. Also, as noted below, the state of the art at the time of the invention acknowledges CKI from a variety of sources – bovine, yeast, rat, and human.

However, these working examples fail to provide the necessary guidance for making the entire scope of CKI and tau proteins as broadly encompassed by the claims. The specification fails to provide guidance regarding alterations in the amino acid sequence with an expectation of maintaining the ability to maintain CKI specificity and the ability to phosphorylate tau.

While applicant may argue that the specification discloses assays for determining whether or not CKI phosphorylates tau protein, it is noted that even if mutants and variants of CKI maintain tau phosphorylation activity, it is highly unpredictable as to whether or not an inhibitor directed to a mutant/variant of CKI would also inhibit a biologically-relevant CKI polypeptide.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of altering a protein sequence were known at the time of the invention, it was not routine in the art to screen all polypeptides as encompassed by the claims, for those that will maintain the desired activity.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required to make all polypeptides as broadly encompassed by the claims, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Thus, applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole

> would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

[16] This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

[17] The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

[18] Claim(s) 22-23, 26-27, 32, 36, and 38 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Meijer et al. (*Chemistry and Biology* 7:51-63, 2000; reference C1 of the 4/20/06 IDS; "Meijer"), (Chijiwa et al. *J. Biol. Chem.* 264:4924-4927, 1989; "Chijiwa"), Lau et al. (*Current Topics in Medicinal Chemistry* 2:395-415; 2002; "Lau"), Castro et al. (*Expert Opinion on Therapeutic Patents* 10:1519-1527, 2000; reference C7 of the 4/20/06 IDS; "Castro"), Singh et al. (*J. Neurochemistry*

64:1420-1423, 1995; reference C3 of the 4/20/06 IDS; "Singh"), and Kuret et al. (*J. Neurochemistry* 69:2506-2515, 1997; reference C2 of the 4/20/06 IDS; "Kuret"). The claims are drawn to a method of screening for inhibitors of CKI phosphorylation of tau protein.

CLAIM INTERPRETATION: The following comments are provided in order to clarify the examiner's interpretation of the claimed invention. Regarding claim 22, the limitation "...wherein the casein kinase I phosphorylates tau protein at one or more sites selected from..." in claim 22 has been interpreted as encompassing an intrinsic property of a casein kinase I polypeptide. Regarding claims 22 and 32, the limitation of "determining whether...the candidate substance inhibits the phosphorylation of the tau protein at one or more sites..." has been broadly, but reasonably interpreted as meaning determining whether or not the tau protein is phosphorylated by CKI, without requiring identification of the specific residue(s) of the tau protein that is/are phosphorylated. Regarding claim 23, the "casein kinase 1" has been interpreted as encompassing any casein kinase 1 from any source, including mutants and variants of known casein kinase 1 polypeptides in view of the recitation of "derivative of full length casein kinase 1". Regarding claim 27, the "tau protein" has been interpreted as encompassing any tau protein from any source, including mutants and variants of known tau proteins in view of the recitation of "derivative of full length tau protein". Regarding claim 36, the claim has been interpreted as encompassing including a positive control, where "another substrate" would be a known CKI substrate. Regarding

claim 37, the claim has been interpreted as encompassing repeating the active steps of claim 22 using an identified inhibitor.

At the time of the invention, methods for screening for inhibitors of CKI activity were known in the prior art. For example, Chijiwa teaches a method for identifying inhibitors of CKI using casein as a substrate and measuring CKI activity in the presence of varying concentrations of inhibitor compound (p. 4924, column 2 and p. 4925, Table I and Figure 1). Meijer teaches identification of a potent inhibitor of CK1, hymenialdisine, and inhibition of CK1 using analogs thereof (p. 54, Table 2) and shows inhibition of CKI phosphorylation of presenilin-2 by hymenialdisine (p. 54, Figure 3). Meijer further teaches "The kinases responsible for hyperphosphorylation of tau…observed in AD certainly constitute reasonable screening targets" and teaches that CK1 is a "major" kinase in this process (p. 61, column 1, top).

Also, at the time of the invention, it was well-known in the prior art that CKI was a therapeutic target by virtue of its activity of phosphorylating tau. For example, the reference of Lau teaches casein kinase I can phosphorylate tau, is tightly associated with paired helical filaments purified from Alzheimer's disease brains, three CKI isoforms are upregulated in Alzheimer's disease brain, and that CKI may be linked to tau pathology in Alzheimer's disease (p. 401, column 2, top). Lau further teaches "Since tau hyperphosphorylation is believed to be a critical step in neurofibrillary degeneration in AD, tau protein kinases become obvious therapeutic targets" (p. 403, column 2, bottom) and that since tau phosphorylation appears to be the primary contributor of paired helical filament/neurofibrillary tangle formation and microtuble disruption,

inhibition of tau phosphorylation has been proposed as a therapeutic target" (p. 405, paragraph bridging columns 1-2).

Additionally, Castro teaches "...such aberrant phosphorylation of tau, determined by the effects of different protein kinases...appears to compromise on its ability to bind and stabilise microtubules and this may contribute to [Alzheimer's disease] pathology" (p. 1520, column 1, bottom) and that casein kinase I has "been shown to phosphorylate certain tau residues *in vitro*" (p. 1520, column 2, middle). According to Castro, "Although the search for tau protein kinase inhibitors is an active field, at the moment few compounds are known with this inhibitor enzymatic property" (p. 1521, column 2, bottom). With regard to identifying tau phosphorylation inhibitors, Castro teaches that *in vitro* assays using GSK-3 – another tau kinase – have been extended to a high throughput methodology for screening selective inhibitors (p. 1521, column 2, bottom).

At the time of the invention, it was well-known in the prior art that tau is phosphorylated by casein kinase I (CKI) from various eukaryotic sources. For example, Singh teaches human tau protein is phosphorylated by bovine brain, bovine kidney, and yeast CKI (p. 1421, Figures 1 and 3). Also, Kuret identifies a paired helical filament kinase as CKI (p. 2506, abstract), teaches tau phosphorylation by human CKI (p. 2508, Figure 1), and that a CKI- specific inhibitor inhibited a paired helical filament-associated CKI polypeptide (p. 2509, column 2, middle).

The combination *suggests* screening for CKI inhibitors of tau protein, however, there appears to be no *express* teaching of a method of using tau as a substrate in a screening method for CKI inhibitors of tau phosphorylation.

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Meijer, Chijiwa, Lau, Castro, Singh and Kuret to use tau as the substrate in the method of Chijiwa or Meijer. One would have been motivated to do this in order to identify inhibitors of CKI phosphorylation of tau protein because of the teachings of Lau and Castro as described above. One would have had a reasonable expectation of success to combine the teachings of Meijer, Chijiwa, Lau, Castro, Singh and Kuret to use tau as the substrate in the method of Chijiwa or Meijer because of the results of Chijiwa, Meijer, Singh, and Kuret. Therefore, claims 22-23, 26-27, 32, 36, and 38, drawn to a method as described and interpreted above, would have been obvious to one of ordinary skill in the art at the time of the invention.

[19] Claim(s) 24-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meijer, Chijiwa, Lau, Castro, Singh, and Kuret as applied to claims 22-23, 26-27, 32, 36, and 38 above and further in view of Graves et al. (*J. Biol. Chem.* 268:6394-6401; 1993, "Graves"). Claims 24-25 limit the CKI polypeptide of the method of claim 22.

The teachings of Meijer, Chijiwa, Lau, Castro, Singh, and Kuret are set forth above. Of note is that Singh and Kuret acknowledge that CKI from bovine, yeast, and human are able to phosphorylate human tau protein. The combination does not appear to teach or suggest using CKI having the amino acid sequence of SEQ ID NO:1.

Graves teaches cloning of a nucleic acid encoding a rat testis CKI polypeptide (p. 6395-6396) that has a nucleotide sequence (p. 6397) that encodes a polypeptide that is 100% identical to SEQ ID NO:1 herein (see Appendix A sequence alignment).

Graves further teaches recombinant production of this polypeptide (p. 6397, paragraph bridging columns 1-2) and use of the polypeptide in an inhibition assay (p. 6398, Figure 6).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Meijer, Chijiwa, Lau, Castro, Singh, Kuret, and Graves to use the polypeptide of Graves in a CKI inhibitor screening method with tau protein as substrate. One would have been motivated to do this because Graves expressly teaches the use of the polypeptide in an inhibition assay and because Singh and Kuret teach CKI from various sources has the ability to phosphorylate tau protein. One would have had a reasonable expectation of success to combine the teachings of Meijer, Chijiwa, Lau, Castro, Singh, Kuret, and Graves to use the polypeptide of Graves in a CKI inhibitor screening method with tau protein as substrate because of the results of Meijer, Chijiwa, Singh, Kuret, and Graves. Therefore, claims 24-25, drawn to a method as described and interpreted above, would have been obvious to one of ordinary skill in the art at the time of the invention.

[20] Claim(s) 28-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meijer, Chijiwa, Lau, Castro, Singh, and Kuret as applied to claims 22-23, 26-27, 32, 36, and 38 above and further in view of Vitek et al. (US Patent 6,593,512; "Vitek"). Claims 28-29 limit the tau polypeptide of the method of claim 22.

The teachings of Meijer, Chijiwa, Lau, Castro, Singh, and Kuret are set forth above. Of note is that Singh and Kuret use human tau in their phosphorylation assays,

however, there is no express teaching of the nucleic acid or encoded protein sequence of the human tau protein.

Vitek teaches cloning of a nucleic acid encoding a human tau polypeptide (Example 7, beginning at column 12) that has a nucleotide sequence (SEQ ID NO:7) that encodes a polypeptide that is 100% identical to SEQ ID NO:1 herein (see Appendix B sequence alignment). Vitek further teaches recombinant production of this polypeptide (Example 10 beginning at column 14) and use of the polypeptide in an inhibition assay (p. 6398, Figure 6).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Meijer, Chijiwa, Lau, Castro, Singh, Kuret, and Vitek to use the polypeptide of Vitek in a CKI inhibitor screening method with tau protein as substrate. One would have been motivated to do this because Vitek expressly teaches recombinant production of a human tau protein and because the assays of Singh and Kuret use human tau protein. One would have had a reasonable expectation of success to combine the teachings of Meijer, Chijiwa, Lau, Castro, Singh, Kuret, and Vitek to use the polypeptide of Vitek in a CKI inhibitor screening method with tau protein as substrate because of the results of Meijer, Chijiwa, Singh, Kuret, and Vitek. Therefore, claims 28-29, drawn to a method as described and interpreted above, would have been obvious to one of ordinary skill in the art at the time of the invention.

[21] Claim(s) 39 and 41-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Meijer, Chijiwa, Lau, Castro, Singh, and Kuret as applied to claims

22-23, 26-27, 32, 36, and 38 above and further in view of Zhu et al. (*Current Opinion in Chemical Biology* 5:40-45, 2001; "Zhu"). Claim 39 limits the method of claim 22 to using mass spectroscopy. Claims 41-42 limit the screening of the method of claim 22.

The teachings of Meijer, Chijiwa, Lau, Castro, Singh, and Kuret are set forth above. Of note is that Castro teaches the concept of using high throughput assays for identifying tau kinase inhibitors as noted above. The combination does not appear to teach or suggest the use of mass spectroscopy or screening according to claims 41-42.

Zhu teaches "In the past, studies of protein activities have focused on studying a single protein at a time, which is often time-consuming and expensive" (p. 40, abstract). Zhu teaches the use of protein chips for protein kinase assay by, *e.g.,* attaching a substrate to a microwell plate and assaying kinase activity (p. 42, paragraph bridging columns 1-2 and p. 43, Figure 2). According to Zhu, "Coupled with mass-spectrometric identification, protein chips might also have wide application in drug discovery…Proteins and small-molecule ligands can be bound to proteins immobilized on a protein chip and the bound molecules identified using…mass spectroscopy" (p. 43, column 1, bottom).

Therefore, it would have been obvious to one of ordinary skill in the art to combine the teachings of Meijer, Chijiwa, Lau, Castro, Singh, Kuret, and Zhu to use a protein chip and mass spectroscopy in a CKI inhibitor screening method with tau protein as substrate. One would have been motivated to do this because Zhu teaches advantages of using protein chips as noted above and Castro suggests using a high throughput assay for identifying inhibitors of a tau kinase. One would have had a

reasonable expectation of success to combine the teachings of Meijer, Chijiwa, Lau, Castro, Singh, Kuret, and Zhu to use a protein chip and mass spectroscopy in a CKI inhibitor screening method with tau protein as substrate because of the results of Meijer, Chijiwa, Singh, Kuret, and Zhu. Therefore, claims 39 and 41-42, drawn to a method as described and interpreted above, would have been obvious to one of ordinary skill in the art at the time of the invention.

Claim Rejections – Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

[22] Claims 22-23, 26-27, 32, 36, and 38 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6-9 and 12 of US Patent 5,994,084 in view of the teachings of Meijer, Chijiwa, Lau, Castro, Singh and Kuret. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not

patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 22-23, 26-27, 32, 36, and 38 of the instant application are limited to comparing CKI phosphorylation of tau in the presence or absence of a test compound, while the claims of the '084 application imply comparing GSK-3 phosphorylation of tau in the presence or absence of compound.

The teachings of Meijer, Chijiwa, Lau, Castro, Singh and Kuret are set forth above. In view of these teachings, it would have been obvious to one of ordinary skill in the art to substitute GSK-3 with CKI in the assay of claims 6-9 and 12 of the '084 patent. One would have been motivated to do this in order to identify tau phosphorylation inhibitors. One would have had a reasonable expectation of success to substitute GSK-3 in the method of the '084 patent with CKI because of the results of Chijiwa, Meijer, Singh, and Kuret.

[23] Claims 24-25 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6-9 and 12 of US Patent 5,994,084 in view of the teachings of Meijer, Chijiwa, Lau, Castro, Singh, Kuret, and Graves. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably

distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 24-25 of the instant application are limited to comparing CKI phosphorylation of tau in the presence or absence of a test compound, while the claims of the '084 application imply comparing GSK-3 phosphorylation of tau in the presence or absence of compound.

The teachings of Meijer, Chijiwa, Lau, Castro, Singh, Kuret, and Graves are set forth above. In view of these teachings, it would have been obvious to one of ordinary skill in the art to substitute GSK-3 with CKI of Graves in the assay of claims 6-9 and 12 of the '084 patent. One would have been motivated to do this in order to identify tau phosphorylation inhibitors. One would have had a reasonable expectation of success to substitute GSK-3 in the method of the '084 patent with CKI of Graves because of the results of Chijiwa, Meijer, Singh, Kuret, and Graves.

[24] Claims 28-29 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6-9 and 12 of US Patent 5,994,084 in view of the teachings of Meijer, Chijiwa, Lau, Castro, Singh, Kuret, and Vitek. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably

distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 28-29 of the instant application are limited to comparing CKI phosphorylation of tau in the presence or absence of a test compound, while the claims of the '084 application imply comparing GSK-3 phosphorylation of tau in the presence or absence of compound.

The teachings of Meijer, Chijiwa, Lau, Castro, Singh, Kuret, and Vitek are set forth above. In view of these teachings, it would have been obvious to one of ordinary skill in the art to substitute GSK-3 with CKI and use the tau of Vitek in the assay of claims 6-9 and 12 of the '084 patent. One would have been motivated to do this in order to identify tau phosphorylation inhibitors. One would have had a reasonable expectation of success to substitute GSK-3 in the method of the '084 patent with CKI and use the tau of Vitek because of the results of Chijiwa, Meijer, Singh, Kuret, and Vitek.

[25] Claims 39 and 41-42 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6-9 and 12 of US Patent 5,994,084 in view of the teachings of Meijer, Chijiwa, Lau, Castro, Singh, Kuret, and Zhu. An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably

distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); and *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 39 and 41-42 of the instant application are limited to comparing CKI phosphorylation of tau in the presence or absence of a test compound, while the claims of the '084 application imply comparing GSK-3 phosphorylation of tau in the presence or absence of compound.

The teachings of Meijer, Chijiwa, Lau, Castro, Singh, Kuret, and Zhu are set forth above. In view of these teachings, it would have been obvious to one of ordinary skill in the art to substitute GSK-3 with CKI and use the method of Zhu in detecting the phosphorylation of tau in the assay of claims 6-9 and 12 of the '084 patent. One would have been motivated to do this in order to identify tau phosphorylation inhibitors. One would have had a reasonable expectation of success to substitute GSK-3 in the method of the '084 patent with CKI and use the method of Zhu for analyzing tau phosphoryation because of the results of Chijiwa, Meijer, Singh, Kuret, and Zhu.

Conclusion

[26] Status of the claims:

- Claims 22-29, 31-36, 38-46, and 53-54 are pending.
- Claims 31, 33-35, 40, 43-46, and 53-54 are withdrawn from consideration.

- Claims 22-29, 32, 36, 38-39, and 41-42 are rejected.

- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/David J. Steadman/
Primary Examiner, Art Unit 1656

APPENDIX A

```
RATCKID
LOCUS       RATCKID                 1960 BP    mRNA    linear   ROD 12-JUN-1993
DEFINITION  Rat casein kinase I delta mRNA, complete cds.
ACCESSION   L07578
VERSION     L07578.1  GI:294524
KEYWORDS    casein kinase I delta.
SOURCE      Rattus norvegicus (Norway rat)
  ORGANISM  Rattus norvegicus
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Euarchontoglires; Glires; Rodentia;
            Sciurognathi; Muroidea; Muridae; Murinae; Rattus.
REFERENCE   1  (bases 1 to 1960)
  AUTHORS   Graves,P.R., Haas,D.W., Hagedorn,C.H., DePaoli-Roach,A.A. and
            Roach,P.J.
  TITLE     Molecular cloning, expression, and characterization of a
            49-kilodalton casein kinase I isoform from rat testis
  JOURNAL   J. Biol. Chem. 268 (9), 6394-6401 (1993)
   PUBMED   8454611
COMMENT     Original source text: Rattus norvegicus male testis cDNA to mRNA.
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                     THQHIPYRENKNLTGTARYASINTHLGIEQSRRDDLESLGYVLMYFNLGSLPWQGLKA
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                     RGTQEVAPPTPLTPTSHTANTSPRPVSGMERERKVSMRLHRGAPVNVSSSDLTGRQDT
                     SRMSTSQRSRDMASLRLHAARQGARCRPQPRRTTY"
     3'UTR           1581..1960
                     /note="the 3' untranslated region differed in one clone;
                     starting from 1644 a different sequence was found which
                     did not hybridize to testis mRNA"
ORIGIN

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Score:                    2247.00        Matches:         428
Percent Similarity:       100.0%         Conservative:    0
Best Local Similarity:    100.0%         Mismatches:      0
Query Match:              100.0%         Indels:          0
DB:                       6              Gaps:            0

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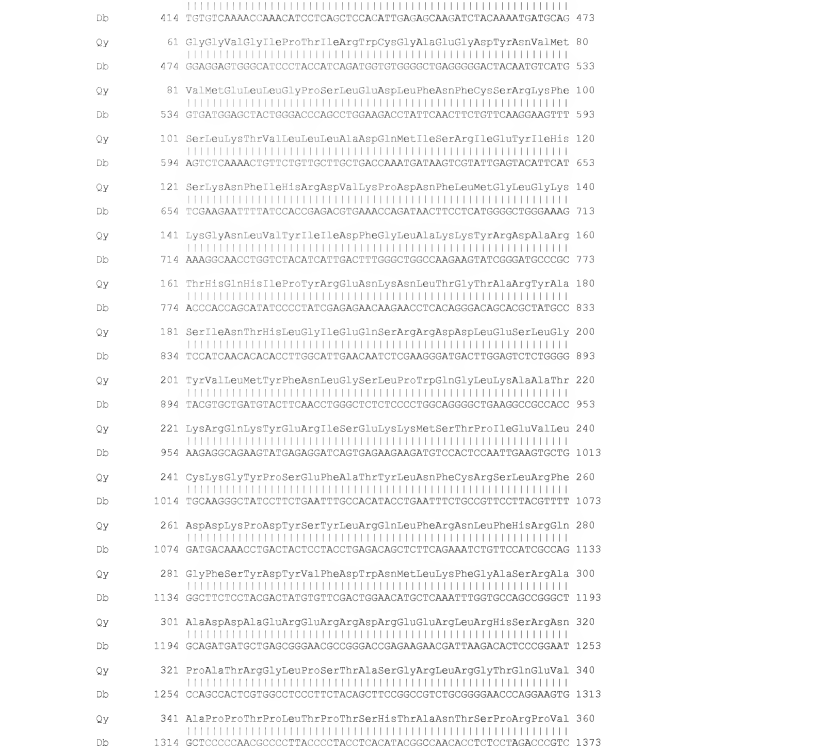
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Qy 221 LysArgGlnLysTyrGluArgIleSerGluLysLysMetSerThrProIleGluValLeu 240
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Qy 241 CysLysGlyTyrProSerGluPheAlaThrTyrLeuAsnPheCysArgSerLeuArgPhe 260
Db 1014 TGCAAGGGCTATCCTTCTGAATTTGCCACATACCTGAATTTCTGCCGTTCCTTACGTTTT 1073
Qy 261 AspAspLysProAspTyrSerTyrLeuArgGlnLeuPheArgAsnLeuPheHisArgGln 280
Db 1074 GATGACAAACCTGACTACTCCTACCTGAGACAGCTCTTCAGAAATCTGTTCCATCGCCAG 1133
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Qy 321 ProAlaThrArgGlyLeuProSerThrAlaSerGlyArgLeuArgGlyThrGlnGluVal 340
Db 1254 CCAGCCACTCGTGGCCTCCCTTCTACAGCTTCCGGCCGTCTGCGGGGAACCCAGGAAGTG 1313
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APPENDIX B

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US-09-517-431E-7
; Sequence 7, Application US/09517431E
; Patent No. 6593512
; GENERAL INFORMATION:
;  APPLICANT: Vitek, Michael P.
;  APPLICANT:  DAWSON, Hana N.
;  APPLICANT:  LORING, Jeanne F.
;  TITLE OF INVENTION: TRANSGENIC MOUSE EXPRESSING HUMAN TAU GENE
;  FILE REFERENCE: 56816-5002
;  CURRENT APPLICATION NUMBER: US/09/517,431E
;  CURRENT FILING DATE:  2000-03-02
;  PRIOR APPLICATION NUMBER: 60/122,691
;  PRIOR FILING DATE: 1999-03-02
;  NUMBER OF SEQ ID NOS: 22
;  SOFTWARE: PatentIn Ver. 2.1
; SEQ ID NO 7
;   LENGTH: 2796
;   TYPE: DNA
;   ORGANISM: Homo sapiens
US-09-517-431E-7

Alignment Scores:
Pred. No.:                1.21e-118       Length:          2796
Score:                    2295.00         Matches:         441
Percent Similarity:       100.0%          Conservative:    0
Best Local Similarity:    100.0%          Mismatches:      0
Query Match:              100.0%          Indels:          0
DB:                       3               Gaps:            0

US-10-562-951-2 (1-441) x US-09-517-431E-7 (1-2796)

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